line 33; page 20, lines 16-22, respectively. Support for amended claim 8 can be found on page 15, line 5. Support for amended claims 9 and 10 can be found on page 14, lines 12-24. Support for amended claim 12 can be found in original claim 39; support for amended claim 28 can be found in original claim 12; and support for amended claims 20-23 and 29-33 find support in original claim 26 and on page 10, lines 6 to 19 (zinc finger proteins under small molecule control).

Support for new claims 87-113 can also be found throughout the specification as filed. In particular, support for new claim 87 can be found in original claim 1; on page 52, lines 8-10 ("establishing an association between a gene and a selected phenotype"); and on page 52 in Example 1. Support for new claims 88-92 can be found, for example, on page 14, lines 4-11 (claims 88 and 89); page 14, lines 12-24 (claim 90); page 31, lines 5-10 (claim 91); and page 14, lines 25-33 (claim 92). Support for new claims 93-108 can be found on page 9, line 21 (regarding exposure to a stimulus); and page 11, line 22; page 15, line 18; and page 45 through page 46 (regarding phenotypes associated with stimuli and assays for these phenotypes). Support for new claims 109-113 can be found, for example, on page 18, line 28 through page 19, line 11 and pages 21-22.

Substantive examination of the newly-presented claims is respectfully requested. If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

Respectfully submitted,

Date: Aug 8, 2001

By: D Pasternak
Dahna S. Pasternak
Registration No. 41,411

ROBINS & PASTERNAK LLP
90 Middlefield Road, Suite 200
Menlo Park, CA 94025
Telephone: (650) 325-7812
Facsimile: (650) 325-7823

Version showing Changes Made to Claims

1. (Amended) A method [of identifying the biological function of a candidate gene] for establishing an association between a first gene and a selected phenotype in a cell, the method comprising the steps of:

(i) selecting a first [candidate] gene, wherein the first gene is not operably linked to heterologous sequences,

(ii) selecting a second gene, wherein the second gene is different from the first gene and wherein the second gene is not operably linked to heterologous sequences;

(iii) providing a first zinc finger protein that binds to a first target site [of the first candidate gene and a second zinc finger that binds to a target site of a second gene] in the first gene and modulates expression of the first gene;

(iv) providing a second zinc finger protein that binds to a second target site in the second gene and modulates expression of the second gene;

(v) culturing a first cell under conditions where the first zinc finger protein contacts the first [candidate] gene [and];

(vi) culturing a second cell under conditions where the second zinc finger protein contacts the second [candidate] gene [wherein the first and the second zinc finger proteins modulate expression of the first and the second candidate genes]; and

(vii) assaying the first and second cells for the [a] selected phenotype, [thereby identifying whether or not the first candidate gene is associated with the selected phenotype] wherein a change in the selected phenotype in the first cell as compared to the second cell indicates an association between the first gene and the selected phenotype.

2. (Amended) The method of claim 1, further comprising providing a third zinc finger protein that binds to [a second target site of the first candidate gene] a third target site in the first gene, wherein the third target site is different than the first target site.

3. Canceled.

4. Canceled.

5. (Amended) The method of claim 1, wherein the first [candidate] gene is partially encoded by an EST [of at least about 200 nucleotides in length].

6. (Amended) The method of claim 1, [wherein the first candidate gene and the second gene are both associated with the selected phenotype] wherein the first and second cells are derived from the same cell type.

7. Canceled.

8. (Amended) The method of claim 1, wherein the first and the second [candidate] genes are

endogenous cellular genes.

9. (Amended) The method of claim 1, wherein [expression of the candidate gene is inhibited by at least about 50%] the modulation is repression.

10. (Amended) The method of claim 1, wherein [expression of the candidate genes is activated by at least about 150%] the modulation is activation.

12. (Amended) The method of claim [1] 11, wherein [expression of the zinc finger proteins is induced by administration of an exogenous agent] the function of the regulatory domain is under small molecule control.

20. (Amended) The method of claim 1, wherein the [first and second zinc finger proteins are encoded by an expression vector comprising a zinc finger protein nucleic acid operably linked to a promoter, and wherein the method further comprises the step of first administering the expression vector to the cell] first zinc finger protein is encoded by a first expression vector comprising a first zinc finger protein-encoding nucleic acid operably linked to a first promoter, and step (v) further comprises administering the first expression vector to the first cell.

21. (Amended) The method of claim 20, wherein the [expression of the zinc finger proteins is under small molecule control] second zinc finger protein is encoded by a second expression vector comprising a second zinc finger protein-encoding nucleic acid operably linked to a second promoter, and step (vi) further comprises administering the second expression vector to the second cell.

22. (Amended) The method of claim [21, wherein expression of the first zinc finger protein and expression of the second zinc finger protein are under different small molecule control ,wherein both the first and second zinc finger proteins are fusion proteins comprising a regulatory domain, and wherein the first and the second zinc finger proteins are expressed in the same cell] 20, wherein the first expression vector further comprises a second zinc finger protein-encoding nucleic acid operably linked to a promoter.

23. (Amended) The method of claim [22, wherein both the first and the second zinc finger proteins comprise a regulatory domain that represses gene expression] 22, wherein the first and second zinc finger protein-encoding nucleic acids are operably linked to the same promoter.

28. (Amended) The method of claim 1, wherein [the target site is upstream of a transcription initiation site of the candidate gene] expression of one or more of the zinc finger proteins is induced by administration of an exogenous agent.

29. (Amended) The method of [claim 1, wherein the target site is adjacent to a transcription initiation site of the candidate gene] claim 22, wherein the first and second zinc finger protein-

encoding nucleic acids are operably linked to different promoters.

30. (Amended) The method of [claim 1, wherein the target site is adjacent to an RNA polymerase pause site downstream of a transcription initiation site of the candidate gene] claim 20, wherein expression of the first zinc finger protein is controlled by a small molecule.

31. (Amended) [A method of identifying the biological function of a candidate gene, the method comprising the steps of:

(i) identifying a plurality of candidate genes;

(ii) providing a first zinc finger protein that binds to a first target site of a first candidate gene;

(iii) culturing a first cell under conditions where the first zinc finger protein contacts the first candidate gene, wherein the first zinc finger protein modulates expression of the first candidate gene;

(iv) determining the expression of pattern of the candidate genes and determining whether or not the first candidate gene is associated with the selected phenotype: and;

(v) repeating steps (ii)-(v) for each candidate gene] The method of claim 21, wherein expression of the second zinc finger protein is controlled by a small molecule.

32. (Amended) The method of claim [31, further comprising providing a second zinc finger protein that binds to a second target site of the first candidate gene] 22, wherein expression of both the first and second zinc finger proteins are controlled by a small molecule.

33. (Amended) The method of [claim 31, wherein at least one of the candidate genes is an EST of at least about 200 nucleotides in length] claim 32, wherein expression of the first zinc finger protein and expression of the second zinc finger protein are controlled by different small molecules.

34 through 86. Canceled.

87. A method for determining the association between a gene and a phenotype of a cell, the method comprising the steps of:

(i) providing first, second and third cells,

(ii) contacting the first cell with a first zinc finger protein that binds to a first target site in the gene and activates expression of the gene;

(iii) contacting the second cell with a second zinc finger protein that binds to a second target site in the gene and represses expression of the gene;

(iv) assaying the first, second and third cells for the selected phenotype; and

(v) comparing the phenotypes exhibited by the first, second and third cells, wherein if the first or second cell exhibits a different phenotype than the third cell, the gene is associated with the phenotype.

88. The method of claim 87, wherein first and second target sites are different.

89. The method of claim 87, wherein first and second target sites are the same.

90. The method of claim 87, wherein the first and second zinc finger proteins are each fused to a regulatory domain.

91. The method of claim 90, wherein the regulatory domains are the same.

92. The method of claim 91, wherein function of the regulatory domain is dependent on a small molecule.

93. The method of claim 87, further comprising the step of exposing the first, second and third cells to at least one selected stimulus prior to assaying for a selected phenotype.

94. The method of claim 93, wherein the phenotype assayed is a change in cell physiology.

95. The method of claim 93, wherein the selected stimulus is serum starvation, growth factor depletion or growth factor stimulation.

96. The method of claim 95, wherein the phenotype assayed is cell proliferation.

97. The method of claim 96, wherein the phenotype assayed is a change in cell cycling.

98. The method of claim 93, wherein the selected stimulus is stress.

99. The method of claim 98, wherein the stress is selected from the group consisting of reducing agents, oxidizing agents, mutagens, DNA synthesis inhibitors, DNA damaging agents, heat shock, cold shock, hypoxia, and altered pressure.

100. The method of claim 99, wherein the DNA damaging agent is a chemical.

101. The method of claim 99, wherein the DNA damaging agent is irradiation.

102. The method of claim 98, wherein the phenotype assayed is a change in cell metabolism.

103. The method of claim 102, wherein the change in cell metabolism is assayed using a transformation assay.

104. The method of claim 93, wherein the selected stimulus is exposure to a pathogen.

105. The method of claim 104, wherein the pathogen is a bacterium.

106. The method of claim 104, wherein the pathogen is a virus.

107. The method of claim 104, wherein the pathogen is a unicellular eukaryote.

108. The method of claim 93, wherein the selected stimulus is treatment with a compound.

109. The method of claim 87, wherein the first, second and third cells further comprise an exogenous nucleic acid.

110. The method of claim 109, wherein the exogenous nucleic acid encodes a polypeptide.

111. The method of claim 110, wherein the polypeptide is an endogenous polypeptide.

112. The method of claim 110, wherein the polypeptide is a mutant form of an endogenous polypeptide.

113. The method of claim 87, wherein the association between the gene and the phenotype indicates a biological function of the gene.